UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/459,808	12/13/1999	AVI J. ASHKENAZI	P0978-1C1	1650

7590 05/20/2002

ATTN DIANE L MARSCHANG
GENETECH INC
1 DNA WAY
SOUTH SAN FRANCISCO, CA 940804990

EXAMINER	
ROMEO, DAVID S	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 05/20/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/459,808	ASHKENAZI, AVI J.	
	Examin r	Art Unit	
	David S Romeo	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 February 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41-52 and 59-78* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41-52 and 59-78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *41-52 and 59-78* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5,6,7* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 41-52, 59-78 are pending.

Applicant's election with traverse of the species 5-FU in Paper No. 14 is acknowledged. The traversal is on the ground(s) that the species election is not proper because no such species election was ever raised during prosecution of the present application's parent application. This is not found persuasive because the fact that a requirement for species election was not made in the parent does not preclude the examiner from making a species election in the present application. In any case, upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

The requirement is still deemed proper and is therefore made FINAL.

Claims 41-52, 59-78 are being examined to the extent that they read upon the elected species.

Citations by the examiner are in an alphanumeric format, such as "(a1)", wherein the "a" refers to the reference cited on the Notice of References Cited, PTO-892, and the "1" refers to the Paper No. to which the Notice of References Cited, PTO-892, is attached.

Specification

The preliminary amendment filed 12/13/99 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: neuroblastoma, glioma, and glioblastoma. A preliminary amendment filed with an application does not enjoy the status as part of the original disclosure in an application unless it is referred to in the oath or declaration accompanying the application. Furthermore, the added material is not supported by the original disclosure because the original disclosure only describes the treatment of "glioblastoma multiforme". Although "glioblastoma multiforme" is a type of neuroblastoma, glioma, and/or glioblastoma, not all neuroblastomas, gliomas, and/or glioblastomas are "glioblastoma multiforme". Stedman's Medical Dictionary defines neuroblastoma (nur´o-blas-to´ma) as a malignant neoplasm characterized by immature, only slightly differentiated nerve cells of embryonic type, i.e., neuroblasts; typical cells are relatively small (10 to 15 mum in diameter) with disproportionately large, darkly staining, vesicular nuclei and scant, palely acidophilic cytoplasm; they may be arranged in sheets, irregular clumps, or cordlike groups, as well as occurring individually and in pseudorosettes (with nuclei arranged peripherally about the centrally directed cytoplasmic processes); ordinarily, the stroma is sparse, and foci of necrosis and hemorrhage are not unusual. N.'s occur frequently in infants and children in the mediastinal and retroperitoneal regions (approximately 30% associated with the adrenal glands); widespread metastases to the liver, lungs, lymph nodes, cranial cavity, and skeleton are very common. olfactory n. a rare, often

slowly growing malignant tumor of primitive nerve cells, usually arising in the olfactory area of the nasal cavity.olfactory esthesioneuroblastoma.

Stedman's Medical Dictionary defines glioblastoma multiforme (gll´o-blas-to´ma) as a glioma consisting chiefly of undifferentiated anaplastic cells of glial origin that show marked nuclear pleomorphism, necrosis, and vascular endothelial proliferation; frequently, tumor cells are arranged radially about an irregular focus of necrosis; these neoplasms grow rapidly, invade extensively, and occur most frequently in the cerebrum of adults.grade IV astrocytoma; [G. glia, glue, + blastos, germ, + -oma, tumor].

Stedman's Medical Dictionary defines glioma (glI-o´ma) as any neoplasm derived from one of the various types of cells that form the interstitial tissue of the brain, spinal cord, pineal gland, posterior pituitary gland, and retina. [G. glia, glue, + -oma, tumor] brainstem g. a g., generally an astrocytoma, arising in the medulla, pons, or midbrain. gigantocellular g. a histologic form of glioblastoma with large, often multinucleated, bizarre, tumor cells.giant cell monstrocellular sarcoma of Zülch; mixed g. a glioma comprised of two or more malignant elements, most frequently astrocytoma and oligodendroglioma. nasal g. term for a lesion that is probably not a true neoplasm, but an unusual anomaly consisting of glial tissue with reactive astrocytes, ganglionic neurons, and ependymal cells in small nodules at the base of the nose. g. of optic chiasm a slow-growing tumor, usually an astrocytoma, of the optic chiasm in children. optic nerve g. a g., generally an astrocytoma, involving the optic nerve or chiasm. g. of the spinal cord a glial tumor of the spinal cord, commonly an ependymoma; neoplasms of the spinal cord are relatively rare, but g.'s constitute approximately one-fourth of the total. telangiectatic g.

, g. telangiecto'des a g. in which the stroma has numerous, conspicuous, frequently dilated small blood vessels and capillaries, as well as large, endothelium-rimmed lakes of blood.

Applicant is required to cancel the new matter in the reply to this Office action.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Regarding the following prior rejections, the recitation of neuroblastoma, glioma, and glioblastoma appears to be new matter with respect to the 08584031 parent application of the present application and benefit of the filing date of the 08584031 parent application is denied.

Claims 47-51, 69-74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weller (u15), Pitti (177, cited by Applicants), Chiocca (a15), and Chen (b15).

Weller teaches that commonly used chemotherapy drugs, including 5-FU, synergized with CD95L in inhibiting clonogenic glioma cell survival (page 287, paragraph bridging left and right columns). Studies to delineate a possible suitability of the Apo2L (TRAIL) system for glioma cell targeting are currently in progress (page 291, left column, first full sentence). Weller does not disclose soluble Apo-2L comprising Apo-2L codons 114-281, a glioma animal model, or a glioblastoma animal model.

Pitti describes the expression and purification of soluble Apo-2L comprising Apo-2L codons 114-281 (page 12687, right column, last full paragraph). Soluble Apo-2L comprising Apo-2L codons 114-281 is identical to a polypeptide comprising amino acid residues 114-281 of SEQ ID NO: 1, a polypeptide comprising a fragment or variant of a polypeptide comprising amino acid residues 114-281 of SEQ ID NO: 1, a polypeptide consisting of amino acid residues 114-281 of SEQ ID NO: 1, a polypeptide which is a fragment of a polypeptide comprising amino acid residues 114-281 of SEQ ID NO: 1, a polypeptide which is a fragment of a polypeptide consisting of amino acid residues 1-281 of SEQ ID NO: 1. Should applicant argue that soluble Apo-2L comprising Apo-2L codons 114-281 does not consist of amino acid residues 114-281 of SEQ ID NO: 1 because of some variation at the N- or C-terminus of soluble Apo-2L comprising Apo-2L codons 114-281, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to make a soluble Apo-2L consisting of Apo-2L codons 114-281, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make a soluble Apo-2L consisting of Apo-2L codons 114-281 because that is an active portion of the molecule. It would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to make a fragment of soluble Apo-2L consisting of Apo-2L codons 114-281, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification in order to correlate structure with function of Apo-2L.

Chiocca discloses a glioma animal model (column 42, lines 62-64).

Chen discloses a glioblastoma animal model (column 18, full paragraph 4).

Pitti, Chiocca, and Chen do not teach the treatment of glioma or glioblastoma by administering soluble Apo-2L comprising Apo-2L codons 114-281.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to delineate a possible suitability of the Apo2L (TRAIL) system for glioma cell targeting, as taught by Weller, and to modify that teaching by delineating a possible suitability of soluble Apo-2L comprising or consisting of Apo-2L codons 114-281, as taught by Pitti, comprising administering soluble Apo-2L comprising or consisting of Apo-2L codons 114-281, or an active fragment of soluble Apo-2L consisting of Apo-2L codons 114-281, to a glioma animal model, as taught by Chiocca, or to a glioblastoma animal model, as taught by Chen, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification because soluble Apo-2L comprising or consisting of Apo-2L codons 114-281, or an active fragment of soluble Apo-2L consisting of Apo-2L codons 114-281, is a component of the Apo2L (TRAIL) system and in order to delineate a possible suitability of soluble Apo-2L comprising or consisting of Apo-2L codons 114-281, or an active fragment of soluble Apo-2L consisting of Apo-2L codons 114-281, in the treatment of glioma or glioblastoma.

Weller, Pitti, Chiocca, and Chen do not exemplify delineating a possible suitability of soluble Apo-2L comprising or consisting of Apo-2L codons 114-281, or an active fragment of soluble Apo-2L consisting of Apo-2L codons 114-281, comprising administering soluble Apo-2L comprising or consisting of Apo-2L codons 114-281, or an active fragment of soluble Apo-2L consisting of Apo-2L codons 114-281, to a glioma or glioblastoma animal model, wherein 5-FU is further administered concurrently, sequentially, or otherwise to said animal models. However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to delineate a possible suitability of soluble Apo-2L comprising or consisting of Apo-2L codons 114-281, or an active fragment of soluble Apo-2L consisting of Apo-2L codons 114-

281, comprising administering soluble Apo-2L comprising or consisting of Apo-2L codons 114-281, or an active fragment of soluble Apo-2L consisting of Apo-2L codons 114-281, to a glioma or glioblastoma animal model, as taught by Weller, Pitti, Chiocca, and Chen, and to modify that teaching by further administering 5-FU concurrently, sequentially, or otherwise, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification in order to achieve synergistic inhibition of glioma or glioblastoma cell survival. The invention is prima facie obvious over the prior art.

Claims 47-52, 69-76 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weller (u15), Pitti (177, cited by Applicants), Chiocca (a15), and Chen (b15) as applied to claims 47-51, 69-74 above, and further in view of Davis (e15).

Weller, Pitti, Chiocca, and Chen teach delineating a possible suitability of the Apo2L (TRAIL) system for glioma cell targeting, as discussed above. Weller, Pitti, Chiocca, and Chen do not teach soluble Apo-2L comprising or consisting of Apo-2L codons 114-281, or an active fragment of soluble Apo-2L consisting of Apo-2L codons 114-281, linked to PEG.

Davis discloses that coupling of polypeptides to polyethylene glycol to provides a physiologically active non-immunogenic water soluble polypeptide composition. The polyethylene glycol protects the polypeptide from loss of activity and the composition can be injected into the mammalian circulatory system with substantially no immunogenic response. See the Abstract. Davis does not teach delineating a possible suitability of the Apo2L (TRAIL) system for glioma cell targeting.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to delineate a possible suitability of the Apo2L (TRAIL) system for glioma cell targeting, as taught by Weller, Pitti, Chiocca, and Chen, and to modify that teaching by linking soluble Apo-2L comprising or consisting of Apo-2L codons 114-281, or an active fragment of soluble Apo-2L consisting of Apo-2L codons 114-281, to PEG, as taught by Davis, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification in order to provide a physiologically active non-immunogenic water soluble Apo-2L comprising or consisting of Apo-2L codons 114-281, or an active fragment of soluble Apo-2L consisting of Apo-2L codons 114-281, composition, protected from loss of activity and that can be injected into the mammalian circulatory system with substantially no immunogenic response. The invention is prima facie obvious over the prior art.

Claims 41-52, 59-66, 69-76 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weller (u15), Pitti (177, cited by Applicants), Chiocca (a15), and Chen (b15) as applied to claims 47-51, 69-74 above, and further in view of Davis (e15) as applied to claims 47-52, 69-76 above, and further in view of Lutz (v15) and DiResta (c15).

Weller, Pitti, Chiocca, and Chen and further in view of Davis teach delineating a possible suitability of the Apo2L (TRAIL) system for glioma cell targeting, as discussed above. Weller, Pitti, Chiocca, and Chen and further in view of Davis do not teach delineating a possible suitability of the Apo2L (TRAIL) system for neuroblastoma cell targeting.

Lutz discloses that neuroblastomas undergo spontaneous regression at an unusually high rate. The mechanisms are not clear, but apoptosis may be involved. See page 339, first two

sentences of Abstract. The CD95 system is involved in drug-induced apoptosis in neuroblastoma cells (page 344, right column, full paragraph 2).

DiResta (c15) discloses a neuroblastoma animal model (column 7, full paragraphs 2 and 4).

Lutz and DiResta do not teach delineating a possible suitability of the Apo2L (TRAIL) system for neuroblastoma cell targeting.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to delineate a possible suitability of the Apo2L (TRAIL) system for glioma cell targeting, as taught by Weller, Pitti, Chiocca, and Chen and further in view of Davis, and to modify that teaching by, delineating a possible suitability of the Apo2L (TRAIL) system for neuroblastoma cell targeting in a neuroblastoma animal model, as taught by DiResta, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification because neuroblastomas undergo spontaneous regression at an unusually high rate, and, although the mechanisms are not clear, apoptosis may be involved, and in order to delineate a possible involvement of the Apo2L (TRAIL) system in neuroblastoma spontaneous regression or in order to delineate a possible suitability of the Apo2L (TRAIL) system for neuroblastoma cell targeting in a neuroblastoma animal model. The invention is prima facie obvious over the prior art.

Claims 41-52, 59-78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weller (u15), Pitti (177, cited by Applicants), Chiocca (a15), and Chen (b15) as applied to claims 47-51, 69-74 above, and further in view of Davis (e15) as applied to claims 47-52, 69-76

above, and further in view of Lutz (v15) and DiResta (c15) as applied to claims 41-52, 59-66, 69-76 above, and further in view of Wiley (25, cited by Applicants).

Weller, Pitti, Chiocca, and Chen, and further in view of Davis, and further in view of Lutz and DiResta, teach delineating a possible suitability of the Apo2L (TRAIL) system for glioma, glioblastoma, and neuroblastoma cell targeting, as discussed above. Weller, Pitti, Chiocca, and Chen, and further in view of Davis, and further in view of Lutz and DiResta, do not teach the production of Apo2L in E. coli.

Wiley discloses the production of TRAIL in E. coli (column 12, full paragraph 1). Wiley's TRAIL is identical to the present application's SEQ ID NO: 1. Wiley does not teach delineating a possible suitability of the Apo2L (TRAIL) system for glioma, glioblastoma, and neuroblastoma cell targeting.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to delineate a possible suitability of the Apo2L (TRAIL) system for glioma, glioblastoma, and neuroblastoma cell targeting, as taught by Weller, Pitti, Chiocca, and Chen, and further in view of Davis, and further in view of Lutz and DiResta, and to modify that teaching by producing Apo2L in E. coli, as taught by Wiley, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification because the supply of many eukaryotic proteins which have potential clinical or industrial use is often limited by their low natural availability. Gene cloning and expression in E. coli would provide an abundant source of readily purified Apo2L.

It would have been further obvious to one of ordinary skill in the art at the time of Applicants' invention to administer Wiley's TRAIL that is identical to the present application's

SEQ ID NO: 1, wherein the TRAIL is linked to PEG, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification in order to be able to administer a fully intact and functional molecule.

The invention is prima facie obvious over the prior art.

Claims 47, 51, 69, 74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rieger (w15) in view of Pitti (177, cited by Applicants). Rieger discloses that ten of twelve glioma cell lines are susceptible to APO2L-induced apoptosis. APO2L targeting may be a promising approach for selectively targeting apoptosis to human malignant glioma cells. See the Abstract. APO2L was prepared as described by Pitti (page 124, right column, full paragraph 1). Pitti describes the expression and purification of soluble Apo-2L comprising Apo-2L codons 114-281 (page 12687, right column, last full paragraph). Pitti describes the expression and purification of soluble Apo-2L comprising Apo-2L codons 114-281 (page 12687, right column, last full paragraph). Soluble Apo-2L comprising Apo-2L codons 114-281 is identical to a polypeptide comprising amino acid residues 114-281 of SEQ ID NO: 1, a polypeptide comprising a fragment or variant of a polypeptide comprising amino acid residues 114-281 of SEQ ID NO: 1, a polypeptide consisting of amino acid residues 114-281 of SEQ ID NO: 1, a polypeptide which is a fragment of a polypeptide comprising amino acid residues 114-281 of SEQ ID NO: 1, a polypeptide which is a fragment of a polypeptide consisting of amino acid residues 1-281 of SEQ ID NO: 1. Should applicant argue that soluble Apo-2L comprising Apo-2L codons 114-281 does not consist of amino acid residues 114-281 of SEQ ID NO: 1 because of some variation at the N- or C-terminus of soluble Apo-2L comprising Apo-2L codons 114-

281, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to make a soluble Apo-2L consisting of Apo-2L codons 114-281, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make a soluble Apo-2L consisting of Apo-2L codons 114-281 because that is an active portion of the molecule. It would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to make a fragment of soluble Apo-2L consisting of Apo-2L codons 114-281, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification in order to correlate structure with function of Apo-2L.

Rieger in view of Pitti does not exemplify a method of a treating a mammal having a glioma comprising administering APO2L. However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to induce apoptosis in glioma cell lines using APO2L, as taught by Rieger in view of Pitti, and to modify that teaching by treating a mammal having a glioma comprising administering APO2L with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification in order to selectively target apoptosis to human malignant glioma cells. The invention is prima facie obvious over the prior art.

Claims 41-52, 59-78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rieger (w15) in view of Pitti (177, cited by Applicants) as applied to claims 47, 51, 69, 74 above, and further in view of, Weller (u15), Pitti (177, cited by Applicants), Chiocca (a15), and Chen (b15) as applied to claims 47-51, 69-74 above, and further in view of Davis (e15) as applied to claims 47-52, 69-76 above, and further in view of Lutz (v15) and DiResta (c15) as

applied to claims 41-52, 59-66, 69-76 above, and further in view of Wiley (25, cited by Applicants).

Rieger teaches treating a mammal having a glioma comprising administering APO2L, as discussed above. Rieger in view of Pitti does not teach administering 5-FU concurrently, sequentially, or otherwise in combination with Apo2L. Rieger in view of Pitti does not teach linking Apo2L to PEG. Rieger in view of Pitti does not teach production of Apo2L in E. coli.

Weller, Pitti, Chiocca, and Chen, and further in view of Davis, and further in view of Lutz and DiResta, and further in view of Wiley teach administering 5-FU concurrently, sequentially, or otherwise in combination with Apo2L, linking Apo2L to PEG, and production of Apo2L in E. coli.

It would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to treat a mammal having a glioma comprising administering APO2L, as taught by Rieger in view of Pitti, and to modify that teaching by administering 5-FU concurrently, sequentially, or otherwise in combination with Apo2L, linking Apo2L to PEG, and producing of Apo2L in E. coli, as taught by Weller, Pitti, Chiocca, and Chen, and further in view of Davis, and further in view of Lutz and DiResta, and further in view of Wiley, as discussed above, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to combine these teachings in order to achieve synergistic inhibition of glioma or glioblastoma cell survival, in order to provide a physiologically active non-immunogenic water soluble Apo-2L comprising or consisting of Apo-2L codons 114-281, or an active fragment of soluble Apo-2L consisting of Apo-2L codons 114-281, composition, protected from loss of activity and that can

be injected into the mammalian circulatory system with substantially no immunogenic response, and in order to provide an abundant source of readily purified Apo2L

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 41-52, 59-63, 65, 67-73, 75, 77, 78 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are directed to or encompass an "Apo-2 ligand" or a polypeptide comprising a "fragment or variant" of amino acid residues 114 to 281 of SEQ ID NO: 1. The specification defines the term "Apo-2 ligand" as a polypeptide sequence which includes amino acid residues 114-281, inclusive, residues 41-281, inclusive, residues 15-281, inclusive, or residues 1-281, inclusive, of the amino acid sequence shown in FIG. 1A, as well as biologically active deletional, insertional, or substitutional variants of the above sequences (paragraph bridging pages 7-8). Amino acid sequence variants of Apo-2 ligand can be prepared by introducing appropriate nucleotide changes into the Apo-2 ligand DNA, or by synthesis of the desired Apo-2 ligand polypeptide. Such variants represent insertions, substitutions, and/or deletions of residues within or at one or both of the ends of the intracellular region, the transmembrane region, or the extracellular region, or of the amino acid sequence shown for the full-length Apo-2 ligand in FIG. 1A. Any combination of insertion,

substitution, and/or deletion can be made to arrive at the final construct, provided that the final construct possesses the desired apoptotic activity as defined herein. See paragraph bridging pages 14-15. Variations in the native sequence as described above can be made using any of the techniques and guidelines for conservative and non-conservative mutations set forth in U.S. Pat. No. 5,364,934. These include oligonucleotide-mediated (site-directed) mutagenesis, alanine scanning, and PCR mutagenesis. See page 15, full paragraph 1.

However, the specification and claims do not place any limit on the number of amino acid substitutions, deletions, insertions and/or additions that may be made to SEQ ID NO: 1. Furthermore, the specification and claims do not place any limit on the number of amino acids in the fragment. Thus, the scope of the claim includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. Although the specification states that these types of changes are routinely done in the art, the specification and claim do not provide any guidance as to what changes should be made. Structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, SEQ ID NO: 1 alone is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus.

Claims 59-63, 67-73, 77-78 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method comprising administering a soluble, limitingly defined Apo2L, does not reasonably provide enablement for a method comprising administering a polypeptide consisting of amino acid residues 1-281 of SEQ ID NO: 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The claims are directed to or encompass administration of a polypeptide comprising a transmembrane domain. In general, transmembrane proteins (and some other tightly bound membrane proteins) can be solubilized only by agents that disrupt hydrophobic associations and destroy the lipid bilayer. See Alberts (x15), page 265, full paragraph 2. When the detergent is removed, solubilized membrane proteins become highly insoluble and precipitate. A further complication is that string detergents often unfold proteins. Such solubilized proteins are often of no use for functional studies. See Alberts (x15), paragraph bridging pages 265-266. The specification lacks guidance for, and working examples of, the administration of a transmembrane protein such that the protein remains soluble and active (functional), and does not aggregate. The skilled artisan is left to extensive, random, trail and error experimentation in order to determine how to achieve the desired effects with a transmembrane protein. In view of the breadth of the claims, the limited amount of direction and working examples provided by the inventor, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure, it would require undue experimentation for the skilled artisan to make and/or use the full scope of the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The following claims are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 41-52 are indefinite because they recite the term "Apo-2 ligand" and/or "variant". Because the instant specification does not identify that material element or combination of elements which is unique to, and, therefore, definitive of "Apo-2 ligand" and/or "variant" an artisan cannot determine what additional or material functional limitations are placed upon a claim by the presence of this element.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Unger (d15) discloses that the surface of a liposome may also be modified with a polymer, such as, for example, with polyethylene glycol (PEG), using procedures readily apparent to those skilled in the art. Small liposomes, less than about 100 nm diameter, are prepared to entrap nitrogen gas under pressure. Phase sensitive lipids are selected with gel to liquid crystalline transition temperature of 42.5 degrees centigrade. These are administered intravenously to a patient with glioblastoma multiforme, which is a usually deadly brain tumor. Ultrasonic hyperthermia is applied to the region of the brain tumor through a skull flap which has been previously made surgically. The microbubbles entrapped in the liposomes accumulate in the patient's tumor because of the leakiness of the tumor vessels. The microbubbles are excluded

from the normal brain because of the integrity of the blood-brain barrier. See column 4, lines 61-65, and paragraph bridging columns 11-12.

No claims are allowed.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (703) 305-4050. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 7:30 A.M. TO 4:00 P.M.

IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, GARY KUNZ, CAN BE REACHED ON (703) 308-4623.

IF SUBMITTING OFFICIAL CORRESPONDENCE BY FAX, APPLICANTS ARE ENCOURAGED TO SUBMIT OFFICIAL CORRESPONDENCE TO THE FOLLOWING TC 1600 BEFORE AND AFTER FINAL RIGHTFAX NUMBERS:

BEFORE FINAL (703) 872-9306
AFTER FINAL (703) 872-9307

IN ADDITION TO THE OFFICIAL RIGHTFAX NUMBERS ABOVE, THE TC 1600 FAX CENTER HAS THE FOLLOWING OFFICIAL FAX NUMBERS: (703) 305-3592, (703) 308-4242 AND (703) 305-3014.

CUSTOMERS ARE ALSO ADVISED TO USE CERTIFICATE OF FACSIMILE PROCEDURES WHEN SUBMITTING A REPLY TO A NON-FINAL OR FINAL OFFICE ACTION BY FACSIMILE (SEE 37 CFR 1.6 AND 1.8).

FAXED DRAFT OR INFORMAL COMMUNICATIONS SHOULD BE DIRECTED TO THE EXAMINER AT (703) 308-0294.

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING SHOULD BE DIRECTED TO THE GROUP RECEPTIONIST WHOSE TELEPHONE NUMBER IS (703) 308-0196.

David Romeo

DAVID ROMEO
PRIMARY EXAMINER
ART UNIT 1647

DSR
MAY 18, 2002